Internal -

~~International~~ Electrophysiological Studies

The first full-scale study addressing the CNS effects of cigarette smoking was completed in 1979. The title of the study was: "The Effects of Cigarette Smoking on the Early, Late and After-Discharge Components of the Visual Evoked Response." The study was undertaken because two earlier reports (Hall, et al, 1973; Friedman, et al, 1974) suggested that components of the response are modifiable by cigarette smoking.

The visual evoked response (VER) is a cortically recorded evoked potential (EP) elicited by brief flashes of monochromatic light. Like most EPs, the VER is an averaged response obtained from repeated stimulation. The late components of the response have been shown to be modifiable by exogenous agents. In particular, it was demonstrated that following smoking, the amplitudes of the IV-V component (Hall, et al, 1973) and the VI-VII component (Friedman, et al, 1974) of the response were increased. The purpose of our study was to attempt to replicate and extend the two earlier studies on the VER and smoking.

Eleven volunteers served as subjects for the experiment. They were tested after both overnight and 1 h smoke deprivation. VERs were recorded immediately before and just after smoking one of two experimental cigarettes. The cigarettes differed in nicotine delivery (0.14 and 1.34 mg/cigt) but were relatively invariant in other smoke constituents. A sham smoking control was also included in the study. The cigarettes were smoked on separate days with order of smoking randomized for each subject. In addition to VERs, we also recorded heart rate (pulse) and expired carbon monoxide (CO).

We found that under the 1 h smoke deprivation condition, smoking the 1.34 mg cigarette resulted in ~~our~~ an amplitude increase in three of the four late components of the VER and that there was a trend of an amplitude increase in fourth component. Smoking

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a 0.14 mg cigarette had no effect on the VER. Smoking either cigarette had no effect on the VER when the subjects were overnight smoke deprived.

These results complement those of the Hall and the Friedman groups in that we found amplitude increases in both the IV-V and the VI-VII. However, our results are more robust in that all four of the late components of the VER were enhanced.

In the study just described, we were surprised to find that the amplitudes of the late VER components were increased following smoking when the subjects were 1 h smoke deprived but <u>not</u> when subjects were overnight smoke deprived. We expected that whatever effects we obtained would be magnified the longer the deprivation interval. This issue was addressed in the VER II study. We reasoned that if VER amplitudes were not increased following the smoking of single cigarette when the subjects were overnight smoke deprived, perhaps the response would be increased when the subjects smoked several cigarettes in succession.

To test this hypothesis, we recorded VERs in 7 volunteers prior to and immediately after smoking three cigarettes (1.34 mg/cigt) in succession. The subjects were overnight smoke deprived at the beginning of the experiment. As a control, the subjects sham smoked three unlit cigarettes while overnight smoke deprived.

The results of the study failed to support our hypothesis. A significant <u>decrease</u> in the amplitudes of most VER components was obtained both after smoking <u>and</u> in the control condition. These data indicate that repeated testing, in and of itself, depresses VER amplitudes. The data further indicate that cigarette smoking under overnight deprivation conditions do not reverse this depressant effect.

A study entitled "Long-Term Smoke Deprivation and the Electrical Activity of the Brain" sought to determine what, if any, changes would occur in the VER when people stopped smoking. Previous studies using smoke deprivations of 12 and 36 h had suggested that VER amplitudes are depressed relative to smoking baselines (Hall, et al, 1973; Friedman, et al, 1974). We (1) wanted to replicate these findings and (2) extended

the deprivation period for days or weeks by using people who, for various reasons, were giving up smoking. We also tested a group of non-smoking control subjects in order to assess the stability of the VER over time, relative to quitters.

Our hypotheses were that if the cessation of cigarette smoking resulted in a permanent reduction in VER amplitudes, this would indirectly comply a return to some kind of pre-smoking baseline. That is, the responses were depressed before the person ever began to smoke. If, on the other hand, the VER remained depressed for some period of time and then gradually recovered to pre-quitting levels, this would indirectly suggest a withdrawal phenomenon of some ~~time~~ kind.

Finally, we were interested in some of the behavioral phenomena associated with smoking cessation. In particular, we were interested in changes in appetite, sleep and mood

The subjects used in this experiment were 12 volunteers, sever of whom were smokers who, for one reason or another expressed a desire to quit (quitters), and five of whom were non-smokers. Pre-quitting measures (VER, mood scale, etc.) were taken on the day before the quitters stopped smoking. We then repeated the experiments one, two and three days post-quitting. Next, we repeated the experiment one week post-quitting. Thereafter, most subjects were tested at monthly intervals. An identical schedule was followed for the non-smokers.

There were no dramatic changes in the VER post-quitting. One day post-quitting, we found a transient (one day) increase in the latency of one VER component in the quitters. This, however, could be statistical artifact due to the large number of tests that were performed. Amplitudes remained remarkably stable post-quitting, contradicting the finding of other laboratories (Hall, et al, 1973; Friedman, et al, 1984).

The mood scale indicated that there were no mood changes after quitting for the first several days post-quitting. For the several days after post-quitting, the quitters reported feeling more tired and irritable. By one week post-quitting, these symptoms had

largely disappeared. The most notable change post-quitting was appetite increase, where the quitters reported cravings for high calorie foods such as sweets and potato chips.

In summary, quitting resulted in no remarkable changes in the VER. The only significant changes were in sleep patterns and behaviors.

Taken as a group, these studies indicate that under certain conditions, changes in the VER can be detected after smoking (e.g., amplitude increases). However, the VER suffers from high inter- and intra-subject variability. This means that it is often difficult to replicate previous findings. For this and other reasons, we abandoned VER studies and undertook studies on auditory evoked potentials (AEPs).

The AEP is cortically recorded evoked potential elicited by brief presentations of pure tone pips delivered through headsets. Like most other EPs, the AEP is an averaged response obtained by repeated stimulation. The AEP waveform is considerably easier to measure in that it has far fewer components than the VER. Hence, we believed it would be more reproducible, and therefore, more reliably analyzed.

At the time the study was conducted, we only knew of two experiments on the effects of nicotine or smoking on the AEP. In an animal experiment (~~Griha~~ Guha & Pradhan, 1976), it was found that low systematic doses of nicotine increased AEP amplitudes while higher doses and intra-cerebral administration depressed amplitudes. In the only human study of that time, it was found that cigarette smoking tended to depress AEP amplitudes (Friedman, et al, 1974). Since VERs are enhanced, while AEPs are depressed by smoking, we thought that smoking might be ~~excreting~~ exerting a selective rather than a generalized effect on the brain. We were also interested in whether any effects on the AEP were influenced by smoke deprivation. Finally, we wanted to compare the response in smokers and non-smokers.

Ten smokers and 10 non-smokers were tested in the study. The smokers were tested when they were not smoke deprived and again when they were overnight smoke deprived. The test cigarette delivered 1.34 mg/cigt nicotine.

nicotine delivery cigarette (0.14 mg/cigt), or sham smoke an unlit. The deprivation

conditions were overnight smoke deprived and not smoke deprived. Thus, each subject was tested six times (i.e., 3 smoking x 2 deprivation conditions). The stimuli for eliciting the BAEPs were clicks delivered through headphones at a rate of 11/sec. BAEPs were recorded before and just after smoking or sham smoking.

We found that cigarette smoking had no effect on the amplitudes of any components of the BAEP. We observed a statistically significant latency increase in one component (peak V). However, this increase was obtained for the low nicotine, high nicotine and sham smoking conditions, indicating that smoking was not responsible for the latency increase. From these data, we concluded that the BAEP is not modified by cigarette smoking.

Up to this point (early 1981), we still had no reliable measure to assess the effects of cigarette smoking on the CNS. This changed dramatically when we came across an EP called the pattern reversal evoked potential (PREP). The PREP is a type of VER which uses a pattern displayed on a video monitor as a stimulus. The pattern, in this case, is a black and white checkerboard. As the name implies, the positions of the black and white checks reverse. The rate of reversal is usually about two per second. The waveform of interest is an averaged response obtained from 100-200 reversals.

The beauty of the PREP is that it is remarkably stable and reproducible both within and between individuals. For this reason, it has become a standard tool of neurologists for assessing the health of the CNS. In particular, it has proven to be highly effective in assessing demyelinating diseases such as multiple sclerosis (Milner, et al, 1974).

When we began our work on the PREP in mid-1980, little was known about the effects of exogenous agents (e.g., drugs) on the PREP. Therefore, we had no idea how modifiable the response was by such agents. In particular, there had been no studies on the effects of cigarette smoking on the PREP.

Our first study, then, was to determine whether the PREP would be modified in some manner by cigarette smoking. The question asked was simply: "What would the post-smoking PREP look like relative to the pre-smoking baselines?"

Ten volunteers who were regular smokers participated in the study. At the time of testing, they were overnight smoke deprived. The cigarettes that were used varied in nicotine delivery, 0.14 and 1.34 mg/cigt) but were relatively invariant in the delivery of other smoke constituents.

On separate occasions, the subjects were required to smoke the 0.14 mg cigarette, the 1.34 mg cigarette, or to sham smoke an unlit cigarette. Baseline PREPs were recorded just prior to smoking and post-smoking. PREPs were recorded immediately after smoking. A controlled smoking procedure was used where the experimenter specified how to puff, when to puff, and how many puffs to take. This was done to ensure that the cigarettes were, as much as possible, smoked in the same way.

Three components of the PREP waveform were measured: N_1, P_1 and N_2. N and P refer to polarity being respectively negative and positive. The subscripts refer to the ordinal position of the component with N, for example, occurring before N_2. Two parameters, latency and amplitude, of each component were evaluated. Latency is a time parameter and refers to how soon after stimulus presentation (in this case, a pattern reversal) a component occurs. Amplitude is a size parameter indicating how large a component was. In this experiment, the amplitude of a component was measured relative to a zero or isoelectric baseline.

An analysis of the data revealed that following the smoking of the 1.34 mg cigarette, there was a statistically significant decrease in the amplitude of the N_1 component. No statistically significant effects were obtained on N_1 following the smoking of the 0.14 mg cigarette or following sham smoking.

Statistically significant decreases in the latency of the P_1 component were obtained following the smoking of the 1.34 mg cigarette. Smoking the 0.14 mg cigarette

and sham smoking had no statistically significant effect on P_1 latency. Smoking had no effect on other latency and amplitude values.

One other finding is of note. At the time we conducted the study, we thought we observed an additional component in the baseline (i.e., smoke deprived) PREP. This component appeared to be a peak between P_1 and N_2. This component seemed to disappear after smoking. We had no idea at the time what this component represented. After nearly a dozen years of additional experience recording the response, two possibilities emerged.

The first possibility, given its latency (~125 msec) is that it is a depressed N_2 which recovers after smoking. The second possibility has to do with smoke deprivation inducing slow waves in the EEG. If the amount of averaging is insufficient, slow waves may remain in the averaged PREP waveform and may appear as an additional component. Naturally, after smoking, the slow waves would diminish, and the additional component would seemingly disappear.

The data, taken as a whole, indicate the PREP can be used to study the effects of cigarette smoking on the CNS. Furthermore, the effects we observed appeared to be due to nicotine, since only the 1.34 mg nicotine cigarette produced statistically significant difference.

A question that immediately arose from the previous study was if mild CNS stimulants other than nicotine would also have an effect on the PREP? The logical choice for a comparable mild CNS stimulant was caffeine.

Ten volunteers participated in the study. All were non-smokers, but regularly consumed caffeine in several different forms. The tests were conducted in the morning following overnight abstinence from all caffeine containing substances (e.g., coffee, tea, cola, chocolate, certain headache preparations, etc.).

Baseline PREPs were first recorded in all subjects. The subjects were then given capsules containing 300 mg caffeine (i.e., the amount of caffeine in about two cups of

strong coffee) or fructose (a sugar derived from fruit). Post-ingestion was recorded 1 h later.

Caffeine ingestion produced a statistically significant decrease in the latency of the N_1 component of the PREP. Caffeine also produced a statistically significant decrease in the latency of P_1. No statistically significant effects were observed following fructose ingestion.

The effects observed with caffeine were, in some respects, similar to the effects produced by nicotine. For example, P_1 latency decreased in both cases. However, caffeine ingestion also resulted in a decrease in N_1 latency, while nicotine resulted in a decrease in N_1 amplitude.

Our third PREP study was entitled: "Sustained Stimulation and Patter Reversal Evoked Potential: Smoking Effects."